Alston & Bird

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

MAY 20 2002

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.05.2002
Applicant's or agent's file reference: 4848-37-1 204836	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/41070	04/10/2000	04/10/1999

Applicant
SHEARWATER POLYMERS, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

DOCKETED
By
Date 5-20-02

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4848-37-1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/41070	04/10/2000	04/10/1999
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant SHEARWATER POLYMERS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/05/2001	16.05.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vogt, T Telephone No. +49 89 2399 8477

Form PCT/IPEA/409 (cover sheet) (January 1994)

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-23	as originally filed	

Claims, No.:

1-25	with telefax of	28/12/2001

Drawings, sheets:

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 5-7, 20-25.

because:

   ☒ the said international application, or the said claims Nos. 5-7 (see point I), and 20-25 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-4, 8-19

	No:	Claims 25
Inventive step (IS)	Yes:	Claims 14, 15
	No:	Claims 1-4, 8-13, 16-25
Industrial applicability (IA)	Yes:	Claims 1-4, 8-19
	No:	Claims 20-25

2. Citations and explanations
see separate sheet

I Amendments.

The applicant submitted a new set of claims 1-25 with the telefax of 28.12.2001.
Claim 4 appears to be inherently disclosed in the specification. It is noted that the method of preparation of a compound is not considered to be restrictive for a claim to a compound. New claim 4 therefore appears to be redundant.
The examiner could not find a basis in the application as originally filed for the technical features of new claims 5-7. These claims are therefore ignored (Rule 70.2(c) PCT).

The remaining amendments do not add subject matter that extend beyond the subject matter of the application as originally disclosed, and consequently meet the requirements of Art. 19 PCT.

II Priority.

The present application validly claims priority from the filing date of US-applications 60/166589 (19.11.1999) and 60/157503 (04.10.1999).

III No opinion.

The subject matter of present claims 5-7 is not in line with Art. 19 PCT and therefore excluded from the substantive examination.

Claims 20-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V Reasoned Statement.

Subject matter of the present application.
The provision of conjugates comprising a peptide and a water soluble non-peptidic polymer, wherein the peptide is selected from biphalin or DPDPE (circular [D-Pen^2, D-Pen^5] enkephalin), pharmaceutical compositions comprising the same and the medical use thereof.

Cited prior art documents (Rule 64(1) PCT).

D1: WITT ET AL. (08.2001) J. PHARM. EXP. THERAPEUT., AM. SOC. PHARM. 298, 848-856.
D2: WO 95 00162 A
D3: WO 91 16929 A
D4: US-A-5 932 462
D5: US-A-5 681 811
D6: WO 00 78302 A
D7: WO 01 12230 A

D1 does not form part of prior art under Rule 64(1)or (3) PCT.
D6 and D7 do not form part of the prior art under Rule 64(1) PCT.

Novelty (Art. 33(2) PCT).

D2 relates to conjugates of peptides with non-antigenic polymers (eg. PEG, cf. claims). D2 states that this modification results in a longer lifetime. The problem solved by D2 is to control the number and location of polymers attached to a peptide, to make sure that the bio-activity of these peptides is not hampered by steric hindrance of the covalently attached polymer (cf. p. 2). D2 solves this problem by making sure that the polymer can only attach to one of the termini of the peptide. Peptides suitable for the invention of D2 are: dynorphin A, neo-endorphins, and opioid peptides (p. 7, l. 28-30). In example 6 of D2, dynorphin A and two endorphin derivatives are conjugated to PEG-5K.

D3 does not appear to contain information relevant to the present application.

D4 discloses multi-armed mono functional PEG for conjugation to proteins to increase the blood circulation time thereof (cf. claims). D4 mentions that thousands of proteins and enzymes can be modified with the multi-armed mono functional PEG and mentions dynorphin in particular (col. 36, l. 42). D4 anticipates the addition of its conjugates to the blood stream and thereby anticipates the subject matter of present claim 25.

D5 discloses conjugates of bio-active agents with a non-peptidic polymer characterised in that the polymer comprises a hydrophilic and a lipophilic moiety (cf. claims). D5 anticipates endorphins, enkephalins (cf. claims 37-47).

To summarize: the subject matter of claim 25 lacks novelty over the cited prior art documents (Art. 33(2) PCT).

Claims 1-4 and 8-24 contain features which alone or in combination with the claims to which they refer do not appear to have been disclosed in the cited prior art. The subject matter of said claims therefore appears to be novel (Art. 33(2) PCT).
The applicant is referred to point I for claims 5-7.

Inventive step (Art. 33(3) PCT).
Claims 1-15 relate to conjugates between a non-peptidic polymer and biphalin or DPDPE.
Having regard to closest prior art D2 the problem solved by the said claims can be seen as the provision of further peptides to conjugate to non-peptidic polymers.
In view of the fact that D2 anticipates 'opioid peptides' in general, the mere provision of further known peptides interacting with opioid receptors cannot be considered to be inventive. Hence the conjugates of D1 can only be considered inventive if an unexpected effect is presented. The present application shows by way of experimental evidence that the analgesic effect of biphalin and DPDPE can be enhanced by covalently modifying the peptides with PEG. This result is surprising because a skilled artisan would not expect PEGylated peptides to be capable of traversing the BBB due to the hydrophilic and bulky nature of the PEG moiety.
However, present claim 1 defines the polymer to be attached to the peptide in very broad terms. In view of the complex nature of the BBB it cannot be reasonably expected that biphalin or DPDPE modified with **any** water soluble non-peptidic polymer (for instance dextran) is capable of traversing the BBB. Consequently, the inventive step can only be acknowledged for those conjugates for which it can be reasonably expected that they solve the problem, namely those of claims 14 and 15.
It follows that the subject matter of claims 1-4, 8-13 lacks an inventive step.

Claims 16, 20 and 21-24 relate to pharmaceutical compositions comprising the conjugate of claim 1, and the medical use thereof.
The arguments raised against claim 1 also apply to these claims. Consequently, the inventive step of claims 16, 20-24 cannot be acknowledged due to the broad definition of the polymer.

Claims 17-19 relate to conjugates comprising: a neuroactive agent, a water soluble non-peptidic polymer and biphalin or DPDPE.
The use of analgesic peptides to target further bioactive components to the brain has not been disclosed or suggested in the cited prior art. However, the same arguments raised against claim 1 also applies to these claims. Consequently the inventive step for the subject matter of claims 17-19 cannot be acknowledged at present.

Because claim 25 lacks novelty it also lacks an inventive step.

To summarize: the subject matter of claims 14 and 15 appears to be inventive, because they contain features which alone or in combination with the claims to which they refer do not appear to have been suggested by any combination of the cited prior art documents. The subject matter of claims 1-4, 8-13 and 16-25 lacks an inventive step.

Industrial applicability (Art. 33(4) PCT).
The conjugates of claims 1-4 and 8-19 can be used in medicine and are therefore industrial applicable.

For the assessment of the present claims 20-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WHAT IS CLAIMED IS:

1. A substantially hydrophilic conjugate comprising a peptide covalently linked to a water-soluble, nonpeptidic polymer wherein said peptide is selected from the group consisting of biphalin and [D-Pen^2, D-Pen^5] enkephalin (DPDPE).

2. The conjugate of Claim 1 having the property of extended analgesic effect in mammals as compared to the native peptide.

3. The conjugate of Claim 1 wherein said water-soluble, nonpeptidic polymer is further characterized by the absence of lipophilic moieties.

4. The conjugate of Claim 1 further characterized in that said nonpeptidic polymer and said peptide are conjugated from solution.

5. The conjugate of Claim 1 further characterized by the absence of noncovalent bonds.

6. The conjugate of Claim 1 further characterized by conjugation of the peptide at at least one terminus thereof.

7. The conjugate of Claim 1 further characterized by conjugation of the peptide at at least one N-terminus thereof

8. The conjugate of Claim 1, wherein said water-soluble, nonpeptidic polymer is polyethylene glycol or a copolymer of polyethylene glycol and polypropylene glycol.

9. The conjugate of Claim 1, wherein said water-soluble, nonpeptidic polymer is polyethylene glycol.

10. The conjugate of Claim 9 wherein said polyethylene glycol is selected from the group consisting of monomethoxypolyethylene glycol, branched polyethylene glycol, polyethylene glycol with degradable linkages in the backbone, homobifunctional polyethylene glycol, heterobifunctional polyethylene glycol, multi-arm polyethylene glycol, pendant polyethylene glycol, and forked polyethylene glycol.

SUBSTITUTE SHEET

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11. The conjugate of Claim 1, wherein said peptide is conjugated to at least one polyethylene glycol molecule.

12. The conjugate of Claim 1, wherein said biphalin has two polyethylene glycol moieties covalently attached.

13. The conjugate of Claim 1 wherein said nonpeptidic polymer is polyethylene glycol having a nominal average molecular weight of about 200 daltons to about 100,000 daltons.

14. The conjugate of Claim 13, wherein said polyethylene glycol has a nominal average molecular weight of about 1000 daltons to about 40,000 daltons.

15. The conjugate of Claim 13, wherein said polyethylene glycol has a nominal average molecular weight of 2000 daltons.

16. A pharmaceutical composition comprising a conjugate according to Claim 1 and a pharmaceutically acceptable carrier for said conjugate.

17. The conjugate of Claim 1 further comprising a neuroactive agent, which may be the same or different from said peptide, conjugated to said non-peptidic polymer.

18. The conjugate of Claim 1 further characterized by a dumbbell structure and further comprising a neuroactive agent, which may be the same or different from said peptide, conjugated to said nonpeptidic polymer.

19. The conjugate of Claim 1 further comprising doxorubicin or an imaging agent conjugated to said nonpeptidic polymer.

20. A method of treating pain comprising administering to a mammal through the general circulation an effective amount of a pharmaceutical preparation comprising the conjugate of Claim 1.

21. A method for delivering a peptide into the brain of an animal through the blood-brain barrier comprising:

providing a pharmaceutical composition comprising a conjugate between a peptide and a water-soluble, non-peptidic polymer wherein the peptide is selected

from the group consisting of biphalin and [D-Pen^2, D-Pen^5] enkephalin (DPDPE); and

administering the composition into the blood stream of an animal.

22. The method of Claim 21, wherein said polymer is selected from the group consisting of copolymers of polyethylene glycol and polypropylene glycol, monomethoxypolyethylene glycol, branched polyethylene glycol, polyethylene glycol with degradable linkages in the backbone, homobifunctional polyethylene glycol, heterobifunctional polyethylene glycol, multi-arm polyethylene glycol, pendant polyethylene glycol, and forked polyethylene glycol.

23. The method of Claim 21, wherein the step of administering the composition comprises pulmonary and intranasal inhalation into said animal.

24. The method of Claim 21, wherein the step of administering the composition is by oral, ocular, buccal, transdermal, or rectal administration.

25. A method for delivering an opioid peptide into the brain of an animal through the blood-brain barrier comprising:

providing a pharmaceutical composition comprising a conjugate between an opioid peptide and a water-soluble, non-peptidic polymer wherein the peptide is selected from the group consisting of dynorphin, enkephalin, endorphin, and endomorphins; and

administering the composition into the blood stream of an animal.

Empfangszeit AMENDED SHEET